REMARKS

I. Status of the Claims

Upon entry of this amendment, claims 1–52 will be pending. As claims 3–10, 16–19 and 24–47 were previously withdrawn by the Examiner, claims 1, 2 11–15, 20–23 and 48–52 are currently at issue. Claims 1 and 48 have been amended. No new matter has been added by way of this amendment.

II. Interviews with Examiner Desai

Applicants' representative (Joshua Marcus) thanks Examiner Desai for the courtesy extended in discussing the current Office Action in the telephone interviews conducted on June 17, 2009 and June 30, 2009. In the first interview, Applicants' representative stated that claim 12 was mistakenly withdrawn. Additionally, in the previous Office Action (mailed September 25, 2008), claims 2, 12 and 21–23 were allowed. Applicants' representative noted that claims 2, 12 and 21–23 were not amended in response to the September 25, 2008 Office Action; and that no reasons were given in the present Office Action for rejection of any of claims 2, 12 and 21–23. Accordingly, Applicants' representative reasoned that these claims should still be allowed. Examiner Desai agreed that claim 12 should be pending and that claims 2, 12, and 21-23 appeared to be allowable. However, the Examiner would not confirm during the interview that these claims were in fact, allowable.

Applicants' representative (Joshua Marcus) called Examiner Desai on June 30, 2009 to inquire further about the enablement rejection. Specifically, Applicant's representative was unclear as to why the enablement rejection was issued in the present Office Action, when in the September 25, 2008 Office Action, the Examiner stated in an enablement rejection for use of the term solvates:

> Hence, applicants must show that solvates can be made, or limit the claims accordingly.

(September 25, 2008 Office Action, p. 3). In response to the September 25, 2008, without conceding the validity of the rejection, and in order to advance prosecution, Applicants deleted the term "solvates" from the claims. However, the enablement rejection for use of the term "solvates" was issued again in the present Office Action. After bringing these facts to the Examiner's attention, the Examiner withdrew the enablement rejection for use of the term "solvates."

II. Enablement Rejection

Claims 1, 11, 13, 14 and 20 are rejected under 35 U.S.C. §112, first paragraph, as lacking enablement because in the Examiner's view, an isolated compound cannot be optionally substituted (*see* Office Action, p. 2). Applicants have amended these claims to delete the phrase "positions 1, 4, 5, and 8 are optionally substituted with halogen, amine, amino, imino, carboxylic acid or amide." Accordingly, this rejection appears to be moot.

Applicants note that the rejection on p. 3 of the Office Action states the *previous rejection under 35 U.S.C. §112 first paragraph over enablement of solvates, anhydrides, tautomers and salts still stands over claims 1, 11, 13, 14 and 20.*" However, the rejection goes on to discuss only "solvates." As conceded by the Examiner in the June 30, 2009 interview summary, the rejection over the term "solvates" was made in error and has been withdrawn.

The Examiner then states that the reagents taught on pp. 11–12 of the specification cannot form all the salts, solvates and anhydrides of the claimed compounds. However, the Examiner fails to recognize that pp. 6–7 of the specification provide ample guidance to one of ordinary skill in the art regarding the reagents and processes for forming salts of the present invention. The Examiner appears to be interpreting the claims to mean that salts have to be isolated from ascidian. However, claims 1 and 2 do not call for salts to be isolated from ascidian, each calls for salts of an isolated compound (*i.e.*, "salts thereof"). Hence, the salts can be formed after isolation of the free compound.

Additionally, claim 2, partially directed to salts of an isolated compound, was allowed in the September 25, 2008 Office Action. The Examiner has not made an argument or offered any reason

as to why one of ordinary skill in the art would not have been able to make the salts of the compounds of claim 1 or 2, after isolation of the free compound, without undue experimentation. Nor has the Examiner provided a reasonable explanation as to why tautomers and anhydrides of the compounds of claim 1 are not adequately enabled (*see* MPEP §2164.04). As such, the Examiner has not met her burden in establishing a *prima facie* case against the rejected claims for lack of enablement of tautomers and anhydrides of the compounds of claim 1.

As stated in the March 25, 2009 response, and reiterated herein, Applicants' position is that one of ordinary skill in the art would have readily known how to make and use tautomers and anhydrides of the present invention. As a general matter, the level of skill in the chemical arts is high. Typically, the ordinary skilled artisan is a Ph.D. chemist with 2–3 years experience. The most basic form of tautomerization, keto–enol tautomerization, is taught in undergraduate organic chemistry classes. For the Examiner's reference, an undergraduate level organic chemistry textbook excerpt, describing how to perform such a reaction, is submitted herewith as Exhibit 1.[1] Graduate level organic chemistry texts teach other mechanisms of tautomerization (*see* Exhibit 2).[2] Accordingly, the tautomerization reactions set out in Exhibits 1 and 2 are within the skill of the ordinary skilled organic chemist.

By the same reasoning, one of ordinary skill in the art would have readily known how to form anhydrides of the claimed compounds of the present invention. As stated above, the ordinary skilled chemist is typically a Ph.D. with 2–3 years experience. Graduate level organic chemistry texts provide great detail as to how to form various anhydrides, depending on a molecule's atomic structure. For the Examiner's convenience, an excerpt from a graduate level organic chemistry textbook is submitted herewith, as Exhibit 3.[3] Exhibit 3 clearly shows that multiple methods of anhydride formation are taught to organic chemistry graduate students. Accordingly, one of ordinary skill in the art would have known how to form the claimed anhydrides of the present invention.

[1] Exhibit 1 published in 1999, which is approximately five years before the present application's filing date (2004).
[2] Exhibit 2 published in 1992, which is approximately twelve years before the present application's filing date (2004).
[3] Exhibit 3 published in 1992, which is approximately twelve years before the present application's filing date (2004)

For at least these reasons, Applicants requests withdrawal of the enablement rejection and reconsideration of the claims.

III. Written Description Rejection

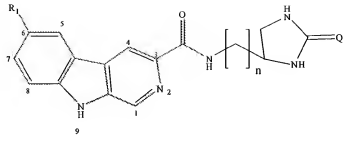
Claims 1, 11, 13, 14 and 20 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner argues that the specification does not have the written description for the clause "*positions 1, 4, 5, and 8 are optionally substituted with halogen, amine, amino, imino, carboxylic acid or amide.*" Without conceding the validity of the rejection, and in order to advance prosecution, this clause has been deleted from the rejected claims. Accordingly, the written description rejection over claims 1, 11, 13, 14 and 20 appears to be moot. Applicants therefore request withdrawal of the written description rejection and reconsideration of the claims.

IV. Claims 2, 12 and 21–23

The Examiner allowed claims 2, 12 and 21–23 in the September 25, 2008 Office Action. In response, Applicants requested rejoinder (under MPEP §821.04(b)) of claims 15–18, 28, 41–42 and 44–47, as each required all the limitations of claim 2. However, this request was not addressed by the Examiner. Additionally, the present Office Action does not provide any reason or argument as to why claims 2, 12 and 21–23 are rejected. Accordingly, Applicants respectfully request that these claims be allowed.

V. Claims 48–52

In the present Office Action, the Examiner rejects claims 48–52, but does not provide a basis, reason or argument for the rejections. Each of these claims is directed to a compound of the formula:



wherein n is 2 to 6; Q is NH or O; R_1 is H or piperazine; and at least one of positions 1, 4, 5, and 8 is substituted with halogen, amine, amino, imino, carboxylic acid or amide.

Claims 48–52 do not call for an isolated compound, and are supported by at least p. 1, ll. 20–22 and p. 5 of the application, as filed. Additionally, the ordinary skilled chemist would have readily known how to make the optional substitutions, to arrive at the claimed compounds. As shown in Exhibit 4,[4] each respective substitution reaction is taught in a graduate level Organic Chemistry textbook. Accordingly, one of ordinary skill in the art would have readily known how to make the compounds of claims 48–52 without undue experimentation.

[4] Exhibit 4 contains excerpts from the same graduate chemistry textbook used for Exhibits 2 and 3.

CONCLUSION

Based on the above amendments and arguments, the subsisting claims are believed to be in condition for allowance, and such action is earnestly solicited. If there are remaining issues that the Examiner believes could be addressed by conducting an interview or entering an Examiner's Amendment, the Examiner is cordially invited to contact the undersigned agent to discuss such issues.

Dated: August 5, 2009

Respectfully submitted,

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Enclosures

- Exhibit 1 – 7 pages
- Exhibit 2– 7 pages
- Exhibit 3 – 3 pages
- Exhibit 4 – 14 pages

Exhibit 1

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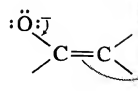
CHAPTER 22

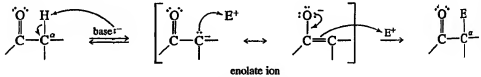


Alpha Substitutions and Condensations of Enols and Enolate Ions

22-1 Introduction

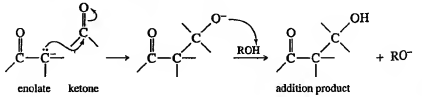
Up to now, we have studied two of the main types of carbonyl reactions: nucleophilic addition and nucleophilic acyl substitution. In these reactions, the carbonyl group serves as an *electrophile* by accepting electrons from an attacking nucleophile. In this chapter, we consider two more types of reactions: substitution at the carbon atom next to the carbonyl group (called alpha substitution) and carbonyl condensations. **Alpha (α) substitutions** involve the replacement of a hydrogen atom at the α carbon atom (the carbon next to the carbonyl) by some other group. Alpha substitution generally takes place when the carbonyl compound is converted to its enolate ion or enol tautomer. Both of these have lost a hydrogen atom at the alpha position, and both are *nucleophilic*. Attack on an electrophile completes the substitution.

Alpha substitution

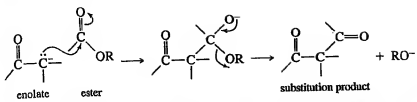


Carbonyl **condensations** are alpha substitutions where the electrophile is another carbonyl compound. From the electrophile's point of view, the condensation is either a nucleophilic addition or a nucleophilic acyl substitution. With ketones and aldehydes, protonation of the alkoxide gives the product of nucleophilic addition. With esters, loss of alkoxide gives the product of nucleophilic acyl substitution.

Condensation: Addition to ketones and aldehydes



Condensation: Substitution with esters



enolate ester substitution product

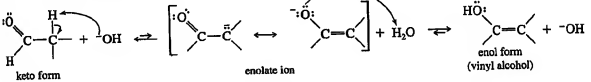
Alpha substitutions and condensations of carbonyl compounds are some of the most common methods for forming carbon–carbon bonds. A wide variety of compounds can participate as nucleophiles or electrophiles (or both) in these reactions, and many useful products can be synthesized. We begin our study of these reactions by considering the structure and formation of enols and enolate ions.

22-2 Enols and Enolate Ions

22-2A Keto–Enol Tautomerism

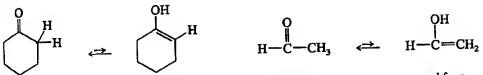
In the presence of strong bases, ketones and aldehydes act as weak proton acids. A proton on the α carbon is abstracted to form a resonance-stabilized **enolate ion** with the negative charge spread over a carbon atom and an oxygen atom. Reprotonation can occur either on the α carbon (returning to the **keto** form) or on the oxygen atom, giving a vinyl alcohol, the **enol** form.

Base-catalyzed keto–enol tautomerism



keto form enolate ion enol form (vinyl alcohol)

In this way, base catalyzes an equilibrium between isomeric keto and enol forms of a carbonyl compound. For simple ketones and aldehydes, the keto form predominates. Therefore, a vinyl alcohol (an enol) is best described as an alternative isomeric form of a ketone or aldehyde. In Section 9-9, we saw that an enol intermediate, formed by hydrolysis of an alkyne, quickly isomerizes to its keto form.

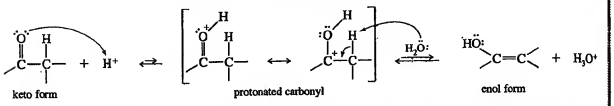


keto form (99.98%) enol form (0.02%) keto form (99.90%) enol form (0.10%)

This type of isomerization, occurring by the migration of a proton and the movement of a double bond, is called **tautomerism,** and the isomers that interconvert are called **tautomers.** Don't confuse tautomers with resonance forms. Tautomers are true isomers (different compounds) with their atoms arranged differently. Under the right circumstances, with no catalyst present, either individual tautomeric form may be isolated. Resonance forms are different representations of the *same* structure, with all the atoms in the same places, showing how the electrons are delocalized.

Keto–enol tautomerism is also catalyzed by acid. In acid, a proton is moved from the α carbon to oxygen by first protonating oxygen and then removing a proton from carbon.

Acid-catalyzed keto–enol tautomerism

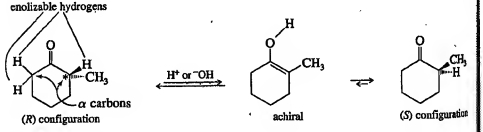


PROBLEM-SOLVING HINT

In acid, proton transfers usually occur by adding a proton in the new position, then deprotonating the old position; in base, by deprotonating the old position, then reprotonating at the new position.

Compare the base-catalyzed and acid-catalyzed mechanisms shown above for keto–enol tautomerism. In base, the proton is removed from carbon, then replaced on oxygen. In acid, oxygen is protonated first, then carbon is deprotonated. Most proton-transfer mechanisms work this way. In base, the proton is removed from the old location, then replaced at the new location. In acid, protonation occurs at the new location, followed by deprotonation at the old location.

In addition to its mechanistic importance, keto–enol tautomerism affects the stereochemistry of ketones and aldehydes. A hydrogen atom on an α carbon may be lost and regained through keto–enol tautomerism; such a hydrogen is said to be **enolizable.** If a chiral carbon has an enolizable hydrogen atom, a trace of acid or base allows that carbon to invert its configuration, with the enol serving as the intermediate. A racemic mixture (or an equilibrium mixture of diastereomers) is the result.



PROBLEM 22-1

Phenylacetone can form two different enols.

(a) Show the structures of these enols.
(b) Predict which enol will be present in the larger concentration at equilibrium.
(c) Give mechanisms for the formation of the two enols in acid and in base.

PROBLEM 22-2

Show each step in the mechanism of the acid-catalyzed interconversion of *(R)*- and *(S)*-2-methylcyclohexanone.

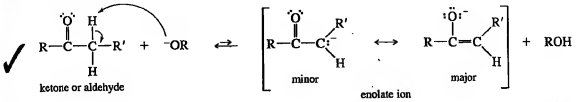
PROBLEM 22-3

When *cis*-2,4-dimethylcyclohexanone is dissolved in aqueous ethanol containing a trace of NaOH, a mixture of cis and trans isomers results. Give a mechanism for this isomerization.

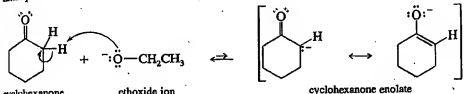
22-2B Formation and Stability of Enolate Ions

A carbonyl group dramatically increases the acidity of the protons on the α-carbon atom because most of the enolate ion's negative charge resides on the electronegative oxygen atom. The pK_a for removal of an α proton from a typical ketone

or aldehyde is about 20, showing that a typical ketone or aldehyde is much more acidic than an alkane or an alkene ($pK_a > 40$), or even an alkyne ($pK_a = 25$). Still, a ketone or aldehyde is less acidic than water ($pK_a = 15.7$) or an alcohol ($pK_a = 16$ to 19) When a simple ketone or aldehyde is treated with hydroxide ion or an alkoxide ion, the equilibrium mixture contains only a small fraction of the deprotonated, enolate form.

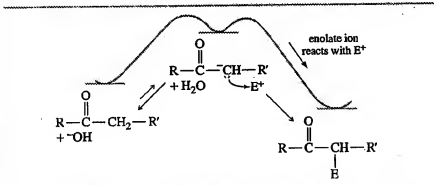


Example



(equilibrium lies to the left)

Even though the equilibrium concentration of the enolate ion may be small, it serves as a useful, reactive nucleophile. When an enolate reacts with an electrophile (other than a proton), the enolate concentration decreases, and the equilibrium shifts to the right (Fig. 22-1). Eventually, all the carbonyl compound reacts via a low concentration of the enolate ion.



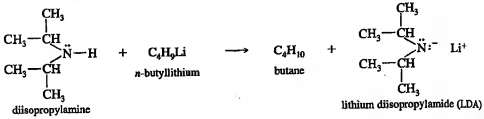
◀ **Figure 22-1**
Reaction of the enolate ion with an electrophile removes it from equilibrium.

PROBLEM 22-4

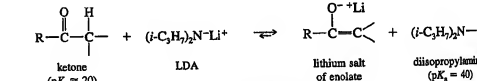
Give the important resonance forms for the enolate ion of
(a) acetone (b) cyclopentanone (c) 2,4-pentanedione

Sometimes this equilibrium mixture of enolate and base won't work, usually because the base (hydroxide or alkoxide) reacts with the electrophile faster than the enolate does. In these cases, we need a base that reacts completely to convert the carbonyl compound to its enolate before adding the elecrophile. Although sodium hydroxide

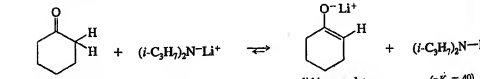
and alkoxides are not sufficiently basic, powerful bases are available to convert a carbonyl compound completely to its enolate. The most effective and useful base for this purpose is lithium diisopropylamide (LDA), the lithium salt of diisopropylamine. LDA is made by using an alkyllithium reagent to deprotonate diisopropylamine.



Diisopropylamine has a pK_a of about 40, showing that it is much *less* acidic than a typical ketone or aldehyde. By virtue of its two isopropyl groups, LDA is a bulky reagent; it does not easily attack a carbon atom or add to a carbonyl group. Thus it is a powerful base, but not a strong nucleophile. When LDA reacts with a ketone, it abstracts the α proton to form the lithium salt of the enolate. We will see that these lithium enolate salts are very useful in synthesis.



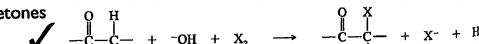
Example



22-3 Alpha Halogenation of Ketones

22-3A Base-Promoted α Halogenation

When a ketone is treated with a halogen and base, an α-halogenation reaction occurs.



Example

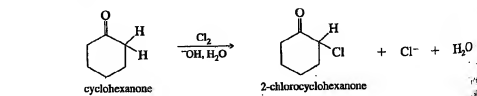


Exhibit 2

ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

FOURTH EDITION

Jerry March

Professor of Chemistry
Adelphi University

A Wiley-Interscience Publication

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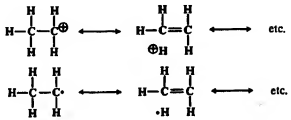
For the other alkyl groups, hyperconjugation is diminished because the number of C—H bonds is diminished and in *t*-butyl there are none; hence, with respect to this effect, methyl is the strongest electron donor and *t*-butyl the weakest.

However, the Baker–Nathan effect has now been shown not to be caused by hyperconjugation, but by differential solvation.[256] This was demonstrated by the finding that in certain instances where the Baker–Nathan effect was found to apply in solution, the order was completely reversed in the gas phase.[257] Since the molecular structures are unchanged in going from the gas phase into solution, it is evident that the Baker–Nathan order in these cases is not caused by a structural feature (hyperconjugation) but by the solvent. That is, each alkyl group is solvated to a different extent.[258]

At present the evidence is against hyperconjugation in the ground states of neutral molecules.[259] However, for carbocations and free radicals[260] and for excited states of molecules,[261] there is evidence that hyperconjugation is important. In hyperconjugation in the ground state of neutral molecules, which Muller and Mulliken call *sacrificial hyperconjugation*,[262] the canonical forms involve not only no-bond resonance but also a charge separation not possessed by the main form. In free radicals and carbocations, the canonical forms display no more charge separation than the main form. Muller and Mulliken call this *isovalent hyperconjugation*:



Even here the main form contributes more to the hybrid than the others.

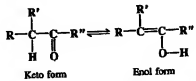
TAUTOMERISM

There remains one topic to be discussed in our survey of chemical bonding in organic compounds. For most compounds all the molecules have the same structure, whether or not this structure can be satisfactorily represented by a Lewis formula. But for many other compounds there is a mixture of two or more structurally distinct compounds that are in rapid equilibrium. When this phenomenon, called *tautomerism*,[263] exists, there is a rapid shift back and forth among the molecules. In most cases, it is a proton that shifts from one atom of a molecule to another.

[256] This idea was first suggested by Schubert; Sweeney *J. Org. Chem.* **1956**, *21*, 119.
[257] Jehre; McIver; Pople; Schleyer *J. Am. Chem. Soc.* **1974**, *96*, 7162; Arnett; Abboud *J. Am. Chem. Soc.* **1975**, *97*, 3865; Glyde; Taylor *J. Chem. Soc., Perkin Trans. 2* **1977**, 678. See also Taylor *J. Chem. Res. (S)* **1985**, 318.
[258] For an opposing view, see Cooney; Happer *Aust. J. Chem.* **1967**, *40*, 1557.
[259] For some evidence in favor, see Laube; Ha *J. Am. Chem. Soc.* **1988**, *110*, 5511.
[260] Symons *Tetrahedron* **1962**, *18*, 333.
[261] Itay; Gokhman; Balasubramanian *Can. J. Chem.* **1960**, *38*, 2508.
[262] Muller; Mulliken *J. Am. Chem. Soc.* **1958**, *80*, 3489.
[263] For reviews, see Toullec *Adv. Phys. Org. Chem.* **1982**, *18*, 1-77; Kol'tsov; Kheifets *Russ. Chem. Rev.* **1971**, *40*, 773-788, **1972**, *41*, 452-467; Forsén; Nilsson in Zabicky, Ref. 246, vol. 2, pp. 157-240.

Keto-Enol Tautomerism[264]

A very common form of tautomerism is that between a carbonyl compound containing an α hydrogen and its enol form:[264a]



Keto form Enol form

In simple cases (R″ = H, alkyl, OR, etc.) the equilibrium lies well to the left (Table 2.1). The reason can be seen by examining the bond energies in Table 1.7. The keto form differs from the enol form in possessing a C—H, a C—C, and a C═O bond where the enol has a C═C, a C—O, and an O—H bond. The approximate sum of the first three is 359 kcal/mol (1500 kJ/mol) and of the second three is 347 kcal/mol (1452 kJ/mol). The keto form is therefore thermodynamically more stable by about 12 kcal/mol (48 kJ/mol) and enol forms cannot normally be isolated.[272a] In certain cases, however, a larger amount of the enol form

TABLE 2.1 The enol content of some carbonyl compounds

Compound	Enol content, %	Ref.
Acetone	6×10^{-7}	265
$PhCOCH_3$	1.1×10^{-6}	266
Cyclopentanone	1×10^{-6}	267
CH_3CHO	6×10^{-5}	268
Cyclohexanone	4×10^{-5}	267
Butanal	5.5×10^{-4}	269
$(CH_3)_2CHCHO$	1.4×10^{-2}	270
Ph_2CHCHO	9.1	271
CH_3COOEt	No enol found[a]	267
CH_3COCH_2COOEt	8.4	272
$CH_3COCH_2COCH_3$	80	272
$PhCOCH_2COCH_3$	89.2	267
$EtOOCCH_2COOEt$	7.7×10^{-3}	267
$NCCH_2COOEt$	2.5×10^{-1}	267

[a]Less than 1 part in 10 million.

[264]The mechanism for conversion of one tautomer to another is discussed in Chapter 12 (reaction 2-3).

[264a]For a treatise, see Rappoport *The Chemistry of Enols*; Wiley: New York, 1990.

[265]Tapuhi; Jencks *J. Am. Chem. Soc.* **1982**, *104*, 5758; Chiang; Kresge; Tang; Wirz *J. Am. Chem. Soc.* **1984**, *106*, 460. See also Hine; Arata *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3089; Guthrie *Can. J. Chem.* **1979**, *57*, 797, 1177; Dubois; El-Alaoui; Toullec *J. Am. Chem. Soc.* **1981**, *103*, 5393; Toullec *Tetrahedron Lett.* **1984**, *25*, 4401; Chiang; Kresge; Schepp *J. Am. Chem. Soc.* **1989**, *111*, 3977.

[266]Keeffe; Kresge; Toullec *Can. J. Chem.* **1986**, *64*, 1224.

[267]Cerio *J. Org. Chem.* **1954**, *19*, 469, 1960; Keeffe, Kresge; Schepp *J. Am. Chem. Soc.* **1990**, *112*, 4862. See these papers for values for other simple compounds.

[268]Chiang; Hojatti; Keeffe; Kresge; Schepp; Wirz *J. Am. Chem. Soc.* **1987**, *109*, 4000.

[269]Bohne; MacDonald; Dunford *J. Am. Chem. Soc.* **1986**, *108*, 7867.

[270]Chiang; Kresge; Walsh *J. Am. Chem. Soc.* **1986**, *108*, 6314; Ref. 269.

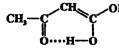
[271]Chiang; Kresge; Krogh *J. Am. Chem. Soc.* **1988**, *110*, 2600.

[272]Moriyasu; Kato; Hashimoto *J. Chem. Soc., Perkin Trans. 2* **1986**, 515.

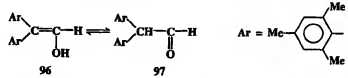
[272a]For reviews on the generation of unstable enols, see Kresge *Pure Appl. Chem.* **1991**, *63*, 213-221; Capon, in Rappoport, Ref. 264a, pp. 307-322.

is present, and it can even be the predominant form.[273] There are three main types of the more stable enols:[274]

1. Molecules in which the enolic double bond is in conjugation with another double bond. Some of these are shown in Table 2.1. As the table shows, carboxylic esters have a much smaller enolic content than ketones. In molecules like acetoacetic ester, the enol is also stabilized by internal hydrogen bonding, which is unavailable to the keto form:



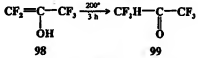
2. Molecules that contain two or three bulky aryl groups.[275] An example is 2,2-dimesitylethenol (**96**). In this case the keto content at equilibrium is only 5%.[276] In cases



96 **97**

such as this steric hindrance (p. 161) destabilizes the keto form. In **96** the two aryl groups are about 120° apart, but in **97** they must move closer together (~109.5°). Such compounds are often called *Fuson-type enols*.[277]

3. Highly fluorinated enols, an example being **98**.[278]



98 **99**

In this case the enol form is not more stable than the keto form (it is less stable, and converts to the keto form upon prolonged heating). It can however be kept at room temperature for long periods of time because the tautomerization reaction (2-3) is very slow, owing to the electron-withdrawing power of the fluorines.

Frequently, when the enol content is high, both forms can be isolated. The pure keto form of acetoacetic ester melts at −39°C, while the enol is a liquid even at −78°C. Each can be kept at room temperature for days if catalysts such as acids or bases are rigorously excluded.[279] Even the simplest enol, vinyl alcohol CH_2=CHOH, has been prepared in the

[273]For reviews of stable enols, see Kresge *Acc. Chem. Res.* **1990**, *23*, 43-48, *CHEMTECH*, **1986**, 250-254; Hart; Rappoport; Biali, in Rappoport, Ref. 264a, pp. 481-589; Hart, *Chem. Rev.* **1979**, *79*, 515-528; Hart; Sasaoka *J. Chem. Educ.* **1980**, *57*, 685-688.

[274]For some examples of other types, see Pratt; Hopkins *J. Am. Chem. Soc.* **1987**, *109*, 5553; Nadler; Rappoport; Arad; Apeloig *J. Am. Chem. Soc.* **1987**, *109*, 7873.

[275]For a review, see Rappoport; Biali *Acc. Chem. Res.* **1988**, *21*, 442-449. For a discussion of their structures, see Kaftory; Nugiel; Biali; Rappoport *J. Am. Chem. Soc.* **1989**, *111*, 8181.

[276]Biali; Rappoport *J. Am. Chem. Soc.* **1985**, *107*, 1007. See also Kaftory; Biali; Rappoport *J. Am. Chem. Soc.* **1985**, *107*, 1701; Nugiel; Rappoport *J. Am. Chem. Soc.* **1985**, *107*, 3669; Nadler; Rappoport *J. Am. Chem. Soc.* **1987**, *109*, 2112; O'Neill; Hegarty *J. Chem. Soc., Chem. Commun.* **1987**, 744; Becker; Andersson *Tetrahedron Lett.* **1987**, *28*, 1323.

[277]First synthesized by Fuson; see for example Fuson; Southwick; Rowland *J. Am. Chem. Soc.* **1944**, *66*, 1109.

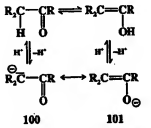
[278]For a review, see Bekker; Knunyants *Sov. Sci. Rev. Sect. B* **1984**, *5*, 145-182.

[279]For an example of particularly stable enol and keto forms, which could be kept in the solid state for more than a year without significant interconversion, see Schelenberg *J. Am. Chem. Soc.* **1968**, *90*, 7008.

gas phase at room temperature, where it has a half-life of about 30 min.[280] The enol $Me_2C{=}CCHOH$ is indefinitely stable in the solid state at −78°C and has a half-life of about 24 hours in the liquid state at 25°C.[281]

The extent of enolization[281a] is greatly affected by solvent,[282] concentration, and temperature. Thus, acetoacetic ester has an enol content of 0.4% in water and 19.8% in toluene.[283] In this case, water reduces the enol concentration by hydrogen bonding with the carbonyl, making this group less available for internal hydrogen bonding. As an example of the effect of temperature, the enol content of pentan-2,4-dione $CH_3COCH_2COCH_3$ was found to be 95, 68, and 44%, respectively, at 22, 180, and 275°C.[284]

When a strong base is present, both the enol and the keto form can lose a proton. The resulting anion (the *enolate ion*) is the same in both cases. Since **100** and **101** differ only in



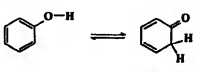
100 **101**

placement of electrons, *they* are not tautomers but canonical forms. The true structure of the enolate ion is a hybrid of **100** and **101** although **101** contributes more, since in this form the negative charge is on the more electronegative atom.

Other Proton-Shift Tautomerism

In all such cases, the anion resulting from removal of a proton from either tautomer is the same because of resonance. Some examples are:[285]

1. Phenol-keto tautomerism.[286]



Phenol Cyclohexadienone

[280]Saito *Chem. Phys. Lett.* **1976**, *42*, 399. See also Capon; Rycroft; Watson; Zucco *J. Am. Chem. Soc.* **1981**, *103*, 1761; Holmes; Lossing *J. Am. Chem. Soc.* **1982**, *104*, 2648; McGarrity; Cretton; Pinkerton; Schwarzenbach; Fluck *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 405 [*Angew. Chem.* **95**, 426]; Rodler; Bloch; Bauder *J. Am. Chem. Soc.* **1984**, *106*, 4029; Capon; Guo; Kwok; Siddhanta; Zucco *Acc. Chem. Res.* **1988**, *21*, 135-140.

[281]Chiu; Lee; Park; Kim *J. Am. Chem. Soc.* **1988**, *110*, 8244.

[281a]For a review of keto-enol equilibrium constants, see Toullec, in Rappoport, Ref. 264a, pp. 323-398.

[282]For an extensive study, see Mills; Beak *J. Org. Chem.* **1985**, *50*, 1216.

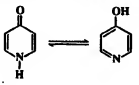
[283]Meyer *Leibigs Ann. Chem.* **1911**, *380*, 212. See also Ref. 272.

[284]Hush; Livett; Peel; Willett *Aust. J. Chem.* **1987**, *40*, 599.

[285]For a review of the use of x-ray crystallography to determine tautomeric forms, see Furmanova *Russ. Chem. Rev.* **1981**, *50*, 775-791.

[286]For reviews, see Ershov; Nikiforov *Russ. Chem. Rev.* **1966**, *35*, 817-833; Forsén; Nilsson, Ref. 263, pp. 168-198.

For most simple phenols this equilibrium lies well to the side of the phenol, since only on that side is there aromaticity. For phenol itself there is no evidence for the existence of the keto form.[287] However, the keto form becomes important and may predominate: (1) where certain groups, such as a second OH group or an N=O group, are present;[288] (2) in systems of fused aromatic rings;[289] (3) in heterocyclic systems. In many heterocyclic compounds in the liquid phase or in solution, the keto form is more stable,[290] although in vapor phase the positions of many of these equilibria are reversed.[291] For example, in the equilibrium between 4-pyridone (**102**) and 4-hydroxypyridine (**103**), **102** is the only form detectable in ethanolic solution, while **103** predominates in the vapor phase.[291]



102 **103**

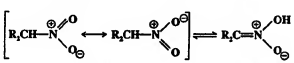
2. Nitroso-oxime tautomerism.

$$R_2CH{-}N{=}O \rightleftharpoons R_2C{=}N{-}OH$$

Nitroso Oxime

This equilibrium lies far to the right, and as a rule nitroso compounds are stable only when there is no α hydrogen.

3. Aliphatic nitro compounds are in equilibrium with aci forms.



Nitro form Aci form

The nitro form is much more stable than the aci form, in sharp contrast to the parallel case of nitroso-oxime tautomerism, undoubtedly because the nitro form has resonance not found in the nitroso case. Aci forms of nitro compounds are also called nitronic acids and azinic acids.

4. Imine-enamine tautomerism.[292]

$$R_2CH{-}CR{=}NR \rightleftharpoons R_2C{=}CR{-}NHR$$

Imine Enamine

[287]Keto forms of phenol and some simple derivatives have been generated as intermediates with very short lives, but long enough for spectra to be taken at 77 K. Lasse; Ripoll; Denis *Tetrahedron Lett.* **1980**, *21*, 463. See also Capponi; Gut; Wirz *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 344 [*Angew. Chem.* **98**, 358].

[288]Ershov; Nikiforov, Ref. 286. See also Highet; Chou *J. Am. Chem. Soc.* **1977**, *99*, 3538.

[289]See, for example, Majerski; Trinajstić *Bull. Chem. Soc. Jpn.* **1976**, *43*, 2648.

[290]For a monograph on tautomerism in heterocyclic compounds, see Elguero; Marzin; Katritzky; Linda *The Tautomerism of Heterocycles*; Academic Press: New York, 1976. For reviews, see Katritzky; Karelson; Harris *Heterocycles* **1991**, *32*, 329-369; Beak *Acc. Chem. Res.* **1977**, *10*, 186-192; Katritzky *Chimia* **1970**, *24*, 134-146.

[291]Beak; Fry; Lee; Steele *J. Am. Chem. Soc.* **1976**, *98*, 171.

[292]For reviews, see Shainyan; Mirskova *Russ. Chem. Rev.* **1979**, *48*, 107-117; Mamaev; Lapachev *Sov. Sci. Rev. Sect. B.* **1985**, *7*, 1-49. The second review also includes other closely related types of tautomerization.

Enamines are normally stable only when there is no hydrogen on the nitrogen ($R_2C{=}CR{-}NR_2$). Otherwise, the imine form predominates.[293]

Ring-chain tautomerism[294] (as in sugars) consists largely of cyclic analogs of the previous examples. There are many other highly specialized cases of proton-shift tautomerism.

Valence Tautomerism

This type of tautomerism is discussed on p. 1134.

[293]For examples of the isolation of primary and secondary enamines, see Shin; Masaki; Ohta *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1657; de Jeso; Pommier *J. Chem. Soc., Chem. Commun.* **1977**, 565.

[294]For a monograph, see Valters; Flitsch *Ring-Chain Tautomerism*; Plenum: New York, 1985. For reviews, see Valters *Russ. Chem. Rev.* **1973**, *42*, 464-476, **1974**, *43*, 665-678; Escale; Verducci *Bull. Soc. Chim. Fr.* **1974**, 1203-1206.

Exhibit 3

ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

FOURTH EDITION

Jerry March

Professor of Chemistry
Adelphi University

A Wiley-Interscience Publication

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Amino Acids and Esters (continued)
resulting oxime or nitroso compound
2-11 From acyl halides and a dialkyl azodicarboxylate
6-5 Hydrolysis of cyanohydrins
6-16 Reaction between aldehydes, ammonia, and carboxylic acids or esters
6-50 Addition of cyanide and ammonium ions to aldehydes or ketones, followed by hydrolysis (Strecker)
8-14 Reaction between imides and NaOBr (Hofmann)

Amino Carbonyl Compounds

0-46 Amination of α-hydroxy ketones
0-47 Transamination of Mannich bases
1-36 Photolysis of acylated arylamines
6-16 Reaction between aldehydes, ammonia, and aldehydes, ketones, or esters (Mannich)
8-13 Rearrangement of ketoxime tosylates (Neber)
8-22 Rearrangement of quaternary ammonium salts (Stevens)
9-23 Oxidation of certain enamines

Amino Ethers

0-18 Alcoholysis of aziridines
5-39 Aminomercuration of alkenes, followed by alcoholysis
6-16 Reaction between aldehydes, amines, and alcohols or phenols (Mannich)

Amino Thiols

0-49 Amination of episulfides
1-9 Sulfurization of aromatic amines (Herz)
6-16 Reaction between an aldehyde, ammonia, and a thiol (Mannich)

Anhydrides

0-27 Reaction of acyl halides with acid salts
0-28 Dehydration of carboxylic acids
0-33 Reaction of acid derivatives with inorganic acids
3-15 From aryl halides and CO
4-11 Acyloxylation of aldehydes
4-31 Reaction between diazonium fluoroborates, CO, and an acid salt
5-5 Addition of carboxylic acids to ketenes
5-22 Free-radical addition of anhydrides to olefins
8-20 Reaction between α-diketones and peroxy compounds (Baeyer–Villiger)
9-10 Oxidation of aromatic rings

Arenes

0-76 Reduction of aryl and benzylic halides
0-78 Hydrogenolysis of benzyl alcohols
0-79 Reduction of benzylic ethers
0-86 Coupling of halides containing aryl groups
0-87 Coupling of aryl halides with organometallic reagents
0-90 Coupling of benzylic alcohols
1-12 Alkylation of aromatic rings (Friedel–Crafts)
1-13 Arylation of aromatic rings (Scholl)
1-22 Diarylation of ketones
1-23 Ring closure of aryl-substituted carbonyl compounds
1-37 Cleavage or rearrangement of alkyl arenes
1-38 Decarbonylation of aromatic aldehydes or deacylation of aromatic ketones
1-39 Decarboxylation of aromatic acids
1-41 Desulfonation of aromatic sulfonic acids
1-42 Dehalogenation of aryl halides
1-44 Hydrolysis of organometallic compounds
2-40 Decarboxylation of α-aryl acids
2-41 Cleavage of tertiary alkoxides
2-45 Cleavage of aryl ketones
2-46 Cleavage of aryl ketones with amide ions (Haller–Bauer)
2-48 Decyanation of aryl nitriles
3-9 Reduction of phenols, phenolic ethers, or phenolic esters
3-10 Reduction of aromatic nitro compounds
3-13 Coupling of organometallic compounds with aryl halides, ethers, and esters

Arenes (
3-16 Cc
3-17 Al
co
4-18 Fr
sal
Ps
4-21 Fr
4-22 Ph
4-24 Rc
4-29 Di
4-30 M
4-33 Cc
4-34 Cc
4-35 Cc
co
4-36 Rc
4-38 Cc
wi
4-41 D
hy
5-20 A
dr
5-51 Tr
6-29 A
dc
7-36 D
ta
8-30 Pl
pl
9-1 A
ri
9-6 C
9-33 D
9-37 R
9-43 R

Aryl Ha

1-11 H
p
1-35 R
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h
1-41 R
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Exhibit 4

ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

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1-6 Amination or Amino-de-hydrogenation[139]

$$ArH + HN_3 \xrightarrow{AlCl_3} ArNH_2$$

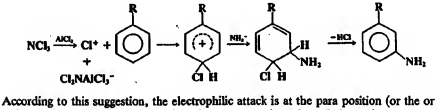
Aromatic compounds can be converted to primary aromatic amines, in 10 to 65% yields, by treatment with hydrazoic acid HN_3 in the presence of $AlCl_3$ or H_2SO_4.[140] Higher yields (> 90%) have been reported with trimethylsilyl azide Me_3SiN_3 and triflic acid F_3CSO_2OH.[141] Tertiary amines have been prepared in fairly good yields (about 50 to 90%) by treatment of aromatic hydrocarbons with N-chlorodialkylamines, by heating in 96% sulfuric acid; or with $AlCl_3$ or $FeCl_3$ in nitroalkane solvents; or by irradiation.[142]

Tertiary (and to a lesser extent, secondary) aromatic amines can also be prepared in moderate to high yields by amination with an N-chlorodialkylamine (or an N-chloroalkylamine) and a metallic-ion catalyst (e.g., Fe^{2+}, Ti^{3+}, Cu^{+}, Cr^{2+}) in the presence of sulfuric acid.[143] The attacking species in this case is the aminium radical ion $R_2\overset{\oplus}{N}H\cdot$ formed by[144]

$$R_2\overset{\oplus}{N}HCl + M^{+} \longrightarrow R_2\overset{\oplus}{N}H\cdot + M^{2+} + Cl^{-}$$

Because attack is by a positive species (even though it is a free radical), orientation is similar to that in other electrophilic substitutions (e.g., phenol and acetanilide give ortho and para substitution, mostly para). When an alkyl group is present, attack at the benzylic position competes with ring substitution. Aromatic rings containing only meta-directing groups do not give the reaction at all. Fused ring systems react well.[145]

Unusual orientation has been reported for amination with halomines and with NCl_3 in the presence of $AlCl_3$. For example, toluene gave predominately meta amination.[146] It has been suggested that initial attack in this case is by Cl^{+} and that a nitrogen nucleophile (whose structure is not known but is represented here as NH_2^{-} for simplicity) adds to the resulting arenium ion, so that the initial reaction is addition to a carbon-carbon double bond followed by elimination of HCl:[147]



According to this suggestion, the electrophilic attack is at the para position (or the ortho, which leads to the same product) and the meta orientation of the amino group arises indirectly. This mechanism is called the *σ-substitution mechanism*.

Aromatic compounds that do not contain meta-directing groups can be converted to diarylamines by treatment with aryl azides in the presence of phenol at −60°C: ArH +

[139]For a review, see Kovacic, in Olah, Ref. 58, vol. 3, 1964, pp. 1493-1506.
[140]Kovacic; Russell; Bennett *J. Am. Chem. Soc.* 1964, *86*, 1588.
[141]Olah; Ernst *J. Org. Chem.* 1989, *54*, 1203.
[142]Bock; Kompa *Angew. Chem. Int. Ed. Engl.* 1965, *4*, 783 [*Angew. Chem.* 77, 807], *Chem. Ber.* 1966, *99*, 1347, 1357, 1361.
[143]For reviews, see Minisci *Top. Curr. Chem.* 1976, *62*, 1-48, pp. 6-16, *Synthesis* 1973, 1-24, pp. 2-12, Sosnovsky; Rawlinson *Adv. Free-Radical Chem.* 1972, *4*, 203-284, pp. 213-238.
[144]For a review of aminium radical ions, see Chow *React. Intermed. (Plenum)* 1988, *1*, 151-262.
[145]The reaction has been extended to the formation of primary aromatic amines, but the scope is narrow: Citterio; Gentile; Minisci; Navarini; Serravalle; Ventura *J. Org. Chem.* 1984, *49*, 4479.
[146]See Kovacic; Lange; Foot; Goralski; Hiller; Levisky *J. Am. Chem. Soc.* 1964, *86*, 1650; Strand; Kovacic *J. Am. Chem. Soc.* 1973, *95*, 2977.
[147]Kovacic; Levisky *J. Am. Chem. Soc.* 1966, *88*, 1000.

$Ar'N_3 \rightarrow ArNHAr'$.[148] Diarylamines are also obtained by the reaction of N-arylhydroxylamines with aromatic compounds (benzene, toluene, anisole) in the presence of F_3CCOOH: $ArH + Ar'NHOH \rightarrow ArNHAr'$.[149]

Direct *amidation* can be carried out if an aromatic compound is heated with a hydroxamic acid in polyphosphoric acid, though the scope is essentially limited to phenolic ethers.[150]

$$ArH + R{-}\overset{\overset{O}{\|}}{C}{-}NH{-}OH \longrightarrow Ar{-}NH{-}\overset{\overset{O}{\|}}{C}{-}R$$

Also see **3-18** and **3-19.**

C. Sulfur Electrophiles

1-7 Sulfonation or Sulfo-de-hydrogenation

$$ArH + H_2SO_4 \longrightarrow ArSO_2OH$$

The sulfonation reaction is very broad in scope and many aromatic hydrocarbons (including fused ring systems), aryl halides, ethers, carboxylic acids, amines,[151] acylated amines, ketones, nitro compounds, and sulfonic acids have been sulfonated.[152] Phenols can also be successfully sulfonated, but attack at oxygen may compete.[153] Sulfonation is often accomplished with concentrated sulfuric acid, but it can also be done with fuming sulfuric acid, SO_3, $ClSO_2OH$, or other reagents. As with nitration (**1-2**), reagents of a wide variety of activity are available to suit both highly active and highly inactive substrates. Since this is a reversible reaction (see **1-41**), it may be necessary to drive the reaction to completion. However, at low temperatures the reverse reaction is very slow and the forward reaction is practically irreversible.[154] SO_3 reacts much more rapidly than sulfuric acid—with benzene it is nearly instantaneous. Sulfones are often side products. When sulfonation is carried out on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur (see **1-40**).

A great deal of work has been done on the mechanism,[155] chiefly by Cerfontain and coworkers. Mechanistic study is made difficult by the complicated nature of the solutions. Indications are that the electrophile varies with the reagent, though SO_3 is involved in all cases, either free or combined with a carrier. In aqueous H_2SO_4 solutions the electrophile is thought to be $H_3SO_4^+$ (or a combination of H_2SO_4 and H_3O^+) at concentrations below about 80 to 85% H_2SO_4, and $H_2S_2O_7$ (or a combination of H_2SO_4 and SO_3) at concentrations higher than this[156] (the changeover point varies with the substrate[157]). Evidence for a change

[148]Nakamura; Ohno; Oka *Synthesis* **1974**, 882. See also Takeuchi; Takano *J. Chem. Soc., Perkin Trans. 1* 1986, 611.

[149]Shudo; Ohta; Okamoto *J. Am. Chem. Soc.* **1981**, *103*, 645.

[150]Wassmundt; Padegimas *J. Am. Chem. Soc.* **1967**, *89*, 7131; March; Bagamko *J. Org. Chem.* **1981**, *46*, 4304.

[151]See Khelevin *J. Org. Chem. USSR* **1964**, *20*, 339, 1173, 1723, **1967**, *23*, 1709, **1968**, *24*, 535.

[152]For reviews, see Nelson, in Olah, Ref. 38, vol. 3, 1964, pp. 1355-1392; Gilbert, *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 62-83, 87-124.

[153]See, for example de Wit; Wokthuis; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 668.

[154]Spryskov *J. Gen. Chem. USSR* **1960**, *30*, 2433.

[155]For a monograph, see Cerfontain *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*; Wiley: New York, 1968. For reviews, see Cerfontain *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 153-165; Cerfontain; Kort *Int. J. Sulfur Chem. C* **1971**, *6*, 123-136; Taylor, in Bamford; Tipper, Ref. 1, pp. 56-77.

[156]Kort; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 24, **1969**, *88*, 860; Maarsen; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1977**, 1003; Cerfontain; Lambrechts; Schaasberg-Nienhuis; Coombes; Hadjiyeorgiou; Tucker *J. Chem. Soc., Perkin Trans. 2* **1985**, 659.

[157]See, for example, Kaandorp; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 725.

D. Halogen Electrophiles

1-11 Halogenation[171] or Halo-de-hydrogenation

$$ArH + Br_2 \xrightarrow{Fe} ArBr$$

1. *Chlorine and bromine.* Aromatic compounds can be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst, most often iron. However, the real catalyst is not the iron itself, but the ferric bromide or ferric chloride formed in small amounts from the reaction between iron and the reagent. Ferric chloride and other Lewis acids are often directly used as catalysts, as is iodine. When thallium(III) acetate is the catalyst, many substrates are brominated with high regioselectivity para to an ortho-para-directing group.[172] For active substrates, including amines, phenols, naphthalene, and polyalkylbenzenes[173] such as mesitylene and isodurene, no catalyst is needed. Indeed, for amines and phenols the reaction is so rapid that it is carried out with a dilute solution of Br_2 or Cl_2 in water at room temperature. Even so, with amines it is not possible to stop the reaction before all the available ortho and para positions are substituted, because the initially formed haloamines are weaker bases than the original amines and are less likely to be protonated by the liberated HX.[174] For this reason, primary amines are often converted to the corresponding anilides if monosubstitution is desired. With phenols it is possible to stop after one group has entered.[175] The rapid room-temperature reaction with amines and phenols is often used as a test for these compounds. Chlorine is a more active reagent than bromine. Phenols can be brominated exclusively in the ortho position (disubstitution of phenol gives 2,6-dibromophenol) by treatment about −70°C with Br_2 in the presence of *t*-butylamine or triethylenediamine, which precipitates out the liberated HBr.[176] Predominant ortho chlorination[177] of phenols has been achieved with chlorinated cyclohexadienes,[178] while para chlorination of phenols, phenolic ethers, and amines can be accomplished with N-chloroamines[179] and with N-chlorodimethylsulfonium chloride $Me_2\overset{\oplus}{S}Cl\ Cl^-$.[180] The last method is also successful for bromination. On the other hand, certain alkylated phenols can be brominated in the meta positions with Br_2 in the super-acid solution SbF_5–HF.[181] It is likely that the meta orientation is the result of conversion by the super acid of the OH group

[171]For a monograph, see de la Mare *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976. For reviews, see Buehler; Pearson *Survey of Organic Synthesis*; Wiley: New York, 1970, pp. 392-404; Brieadlin; McBee, in Olah, Ref. 58, vol. 3, 1964, pp. 1517-1593. For a review of the halogenation of heterocyclic compounds, see Eisch *Adv. Heterocycl. Chem.* 1966, *7*, 1-37. For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 315-318.

[172]McKillop; Bromley; Taylor *J. Org. Chem.* 1972, *37*, 88.

[173]For a review of aromatic substitution on polyalkylbenzenes, see Baciocchi; Illuminati *Prog. Phys. Org. Chem.* 1967, *5*, 1-79.

[174]Monobromination (para) of aromatic amines has been achieved with tetrabutylammonium tribromide: Berthelot; Guette; Desbène; Basselier; Chaquin; Masure *Can. J. Chem.* 1989, *67*, 2061. For another procedure, see Ouaka; Izumi *Chem. Lett.* 1984, 2007.

[175]For a review of the halogenation of phenols, see Britain; de la Mare, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement D*, pt. 1; Wiley: New York, 1983, pp. 522-532.

[176]Pearson; Wysong; Breder *J. Org. Chem.* 1967, *32*, 2358.

[177]For other methods of regioselective chlorination or bromination, see Schmitz; Pagcakopf *J. Prakt. Chem.* 1985, *327*, 998; Watson *J. Org. Chem.* 1985, *50*, 2145; Smith; Butters; Paget; Nay *Synthesis* 1985, 1157, *Tetrahedron Lett.* 1988, *29*, 1319; Kodomari; Takahashi; Yoshitomi *Chem. Lett.* 1987, 1901; Kamigata; Satoh; Yoshida; Matsuyama; Kameyama *Bull. Chem. Soc. Jpn.* 1988, *61*, 2226; de la Vega; Sasson *J. Chem. Soc., Chem. Commun.* 1989, 655.

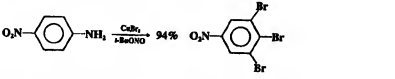
[178]Guy; Lemaire; Guette *Tetrahedron* 1982, *38*, 2339, 2347; Lemaire; Guy; Guette *Bull. Soc. Chim. Fr.* 1985, 477.

[179]Lindsay Smith; McKeer; Taylor *J. Chem. Soc., Perkin Trans. 2* 1987, 1533, 1988, 385, 1989, 1529, 1537. See also Minisci; Vismara; Fontana; Platone; Fuzzi *J. Chem. Soc., Perkin Trans. 2* 1989, 123.

[180]Olah; Ohannesian; Arvanaghi *Synthesis* 1986, 868.

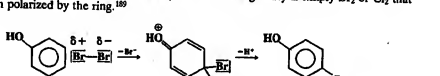
[181]Jacquesy; Jouannetaud; Makani *J. Chem. Soc., Chem. Commun.* 1980, 110.

to the OH_2^+ group, which should be meta-directing because of its positive charge. Bromination and the Sandmeyer reaction (4-25) can be carried out in one laboratory step by treatment of an aromatic primary amine with $CuBr_2$ and *t*-butyl nitrite, e.g.,[182]



Other reagents have been used, among them HOCl,[183] HOBr, and N-chloro and N-bromo amides (especially N-bromosuccinimide and tetraalkylammonium polyhalides[184]). In all but the last of these cases the reaction is catalyzed by the addition of acids. Dibromoisocyanuric acid in H_2SO_4 is a very good brominating agent[185] for substrates with strongly deactivating substituents.[186] Two particularly powerful reagents consist of (1) S_2Cl_2 and $AlCl_3$ in sulfuryl chloride (SO_2Cl_2) (the *BMC reagent*)[187] and (2) dichlorine oxide Cl_2O and a strong acid such as sulfuric.[188] If the substrate contains alkyl groups, side-chain halogenation (4-1) is possible with most of the reagents mentioned, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible.

For reactions in the absence of a catalyst, the attacking entity is simply Br_2 or Cl_2 that has been polarized by the ring.[189]



26

Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, especially chloride ion, accelerate the rate about equally, though if chlorine dissociated into Cl^+ and Cl^-, the addition of chloride should decrease the rate and the addition of acids should increase it. The conjugate base of **26** (4-bromo-2,5-cyclohexadienone) has been detected spectrally in the aqueous bromination of phenol.[190]

When a Lewis-acid catalyst is used with chlorine or bromine, the attacking entity may be Cl^+ or Br^+, formed by $FeCl_3 + Br_2 \rightarrow FeCl_3Br^- + Br^+$, or it may be Cl_2 or Br_2, polarized by the catalyst. With other reagents, the attacking entity in brominations may be Br^+ or a species such as H_2OBr^+ (the conjugate acid of HOBr), in which H_2O is a carrier of Br^+.[191]

[182]Doyle; Van Lente; Mowat; Fobare *J. Org. Chem.* **1980**, *45*, 2570.

[183]For the use of calcium hypochlorite, see Nwaukwa; Keehn *Synth. Commun.* **1989**, *19*, 799.

[184]See Kajigaeshi; Moriwaki; Tanaka; Fujisaki; Kakinami; Okamoto *J. Chem. Soc., Perkin Trans. 1* **1990**, 897, and other papers in this series.

[185]Nitrobenzene is pentabrominated in 1 min with this reagent in 15% oleum at room temperature.

[186]Gottardi *Monatsh. Chem.* **1968**, *99*, 815, **1969**, *100*, 42.

[187]Ballester; Molinet; Castañer *J. Am. Chem. Soc.* **1960**, *82*, 4254; Andrews, Glidewell; Walton *J. Chem. Res. (S)* **1978**, 294.

[188]Marsh; Farnham; Sam; Smart *J. Am. Chem. Soc.* **1982**, *104*, 4680.

[189]For reviews of the mechanism of halogenation, see de la Mare, Ref. 171; de la Mare; Swedland, in Patai *The Chemistry of the Carbon-Halogen Bond*, pt. 1; Wiley: New York, 1973; pp. 490-536; Taylor, in Bamford; Tipper, 3877; Keefer; Andrews *J. Am. Chem. Soc.* **1977**, *99*, 5693; Briggs; de la Mare; Hall *J. Chem. Soc., Perkin Trans. 2* **1977**, 106; Tee; Paventi; Bennett *J. Am. Chem. Soc.* **1989**, *111*, 2233.

[190]Tee; Iyengar; Paventi *J. Org. Chem.* **1983**, *48*, 759. See also Tee; Iyengar *J. Am. Chem. Soc.* **1985**, *107*, 455, *Can. J. Chem.* **1990**, *68*, 1760.

[191]For discussions, see Gilow; Ridd *J. Chem. Soc., Perkin Trans. 2* **1973**, 1321; Rao; Mali; Dangat *Tetrahedron* **1978**, *34*, 205.

With HOCl in water the electrophile may be Cl_2O, Cl_2, or H_2OCl^+; in acetic acid it is generally AcOCl. All these species are more reactive than HOCl itself.[192] It is extremely doubtful that Cl^+ is a significant electrophile in chlorinations by HOCl.[192] It has been demonstrated in the reaction between N-methylaniline and calcium hypochlorite that the chlorine attacking entity attacks the *nitrogen* to give N-chloro-N-methylaniline, which rearranges (as in **1-35**) to give a mixture of ring-chlorinated N-methylanilines in which the ortho isomer predominates.[193]

$FeCl_3$ itself, and also $CuCl_2$, $SbCl_5$, etc.,[194] can give moderate yields of aryl chlorides.[195] The electrophile might be a species such as $FeCl_2^+$, but the reactions can also take place by a free-radical mechanism.[196]

When chlorination or bromination is carried out at high temperatures (e.g., 300 to 400°C), ortho-para-directing groups direct meta and vice versa.[197] A different mechanism operates here, which is not completely understood. It is also possible for bromination to take place by the SRI mechanism, e.g., in the *t*-BuOK-catalyzed bromination of 1,3,5-tribromobenzene.[198]

2. *Iodine.* Iodine is the least reactive of the halogens in aromatic substitution.[199] Except for active substrates, an oxidizing agent must normally be present to oxidize I_2 to a better electrophile.[200] Examples of such oxidizing agents are HNO_3, HIO_3, SO_3, peracetic acid, and H_2O_2.[201] ICl is a better iodinating agent than iodine itself.[202] Among other reagents used have been IF (prepared directly from the elements),[203] benzyltrimethylammonium dichloroiodate (which iodinates phenols, aromatic amines, and N-acylated aromatic amines),[204] and the combination of iodine cyanide ICN and a Lewis acid, which is a good reagent for active substrates.[205] Iodination can also be accomplished by treatment of the substrate with I_2 in the presence of copper salts,[206] $SbCl_5$,[207] silver trifluoromethanesulfonate CF_3SO_3Ag,[208] $HgO–BF_4$,[209] Al_2O_3,[210] $AgNO_3$,[211] Ag_2SO_4,[212] or thallium(I) acetate.[213] The TlOAc method is regioselective for ortho iodination.

The actual attacking species is less clear than with bromine or chlorine. Iodine itself is too unreactive, except for active species such as phenols, where there is good evidence that

[192]Swain; Crist *J. Am. Chem. Soc.* **1972**, *94*, 3195.

[193]Haberfield; Paul *J. Am. Chem. Soc.* **1965**, *87*, 5502; Gassman; Campbell *J. Am. Chem. Soc.* **1972**, *94*, 3891; Paul; Haberfield *J. Org. Chem.* **1976**, *41*, 3170.

[194]Kovacic; Wu; Stewart *J. Am. Chem. Soc.* **1960**, *82*, 1917; Ware; Borchest *J. Org. Chem.* **1961**, *26*, 2267; Commandeur; Mathais; Raynier; Wargell *Nouv. J. Chim.* **1979**, *3*, 385; Makhon'kov; Cheprakov; Rodkin; Beletskaya *J. Org. Chem. USSR* **1988**, *24*, 211; Kodomari; Satoh; Yoshitomi *J. Org. Chem.* **1988**, *53*, 2093.

[195]For a review of halogenations with metal halides, see Kovacic, in Olah, Ref. 58, vol. 4, 1965, pp. 111-126.

[196]Nonhebel *J. Chem. Soc.* **1963**, 1216; Nonhebel; Russell *Tetrahedron* **1969**, *25*, 3493.

[197]For a review of this type of reaction, see Kooyman *Pure. Appl. Chem.* **1963**, *7*, 193-202.

[198]Mach; Bunnett *J. Am. Chem. Soc.* **1974**, *96*, 936.

[199]For reviews of I_2 as an electrophilic reagent, see Pizey, in Pizey *Synthetic Reagents*, vol. 3; Wiley: New York, 1977, pp. 227-276. For reviews of aromatic iodination, see Merkushev *Synthesis* **1988**, 923-937, *Russ. Chem. Rev.* **1984**, *53*, 343-350.

[200]Butler *J. Chem. Educ.* **1971**, *48*, 508.

[201]For a discussion, see Makhon'kov; Cheprakov; Beletskaya *J. Org. Chem. USSR* **1989**, *24*, 2029.

[202]For a review of ICl, see McCleland, in Pizey, Ref. 199, vol. 5, 1983, pp. 85-164.

[203]Rozen; Zamir *J. Org. Chem.* **1990**, *55*, 3552.

[204]See Kajigaeshi; Kakinami; Watanabe; Okamoto *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1349, and references cited therein.

[205]Radnez *Acta Chem. Scand.* **1989**, *43*, 481. For another method, see Edgar; Falling *J. Org. Chem.* **1990**, *55*, 5287.

[206]Baird; Surridge *J. Org. Chem.* **1970**, *35*, 3436; Horiuchi; Satoh *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2691; Makhon'kov; Cheprakov; Rodkin; Beletskaya *J. Org. Chem. USSR* **1986**, *22*, 1003.

[207]Uemura; Onoe; Okano *Bull. Chem. Soc. Jpn.* **1974**, *47*, 147.

[208]Kobayashi; Kumadaki; Yoshida *J. Chem. Res. (S)* **1977**, 215. For a similar procedure, see Merkushev; Simakhina; Koveshnikova *Synthesis* **1980**, 486.

[209]Barluenga; Campos; Gonzáles; Asensio *J. Chem. Soc., Perkin Trans. 1* **1984**, 2623.

[210]Pagni; Kabalka; Boothe; Gaetano; Stewart; Conaway; Dial; Gray; Larson; Luidhart *J. Org. Chem.* **1988**, *53*, 4477.

[211]Sy; Lodge *Tetrahedron Lett.* **1989**, *30*, 3769.

[212]Sy; Lodge; By *Synth. Commun.* **1990**, *20*, 877.

[213]Cambie; Rutledge; Smith-Palmer; Woodgate *J. Chem. Soc., Perkin Trans. 1* **1976**, 1161.

I_2 is the attacking entity.[214] There is evidence that AcOI may be the attacking entity when peroxyacetic acid is the oxidizing agent,[215] and I_3^+ when SO_3 or HIO_3 is the oxidizing agent.[216] I^+ has been implicated in several procedures.[216a] For an indirect method for accomplishing aromatic iodination, see **2-30.**

3. *Fluorine.* Direct fluorination of aromatic rings with F_2 is not feasible at room temperature, because of the extreme reactivity of F_2.[217] It has been accomplished at low temperatures (e.g., −70 to −20°C, depending on the substrate),[218] but the reaction is not yet of preparative significance. Fluorination has also been reported with silver difluoride AgF_2,[219] with cesium fluoroxysulfate $CsSO_4F$[220] with acetyl hypofluorite CH_3COOF (generated from F_2 and sodium acetate),[221] with XeF_2,[222] with an N-fluoroperfluoroalkyl sulfonamide, e.g., $(CF_3SO_2)_2NF$,[223] and with fluoroxytrifluoromethane CF_3OF[224] under various conditions and with various yields, in some cases by electrophilic and in other cases by free-radical mechanisms. However, none of these methods seems likely to displace the Schiemann reaction **(3-24)** as the most common method for introducing fluorine into aromatic rings.

The overall effectiveness of reagents in aromatic substitution is $Cl_2 > BrCl > Br_2 > ICl > I_2$.

OS **I,** 111, 121, 123, 128, 207, 323; **II,** 95, 97, 100, 173, 196, 343, 347, 349, 357, 592; **III,** 132, 134, 138, 262, 267, 575, 796; **IV,** 114, 166, 256, 545, 547, 872, 947; **V,** 117, 147, 206, 346; **VI,** 181, 700; **67,** 222. Also see OS **II,** 128.

E. Carbon Electrophiles In the reactions in this section, a new carbon–carbon bond is formed. With respect to the aromatic ring, they are electrophilic substitutions, because a positive species attacks the ring. We treat them in this manner because it is customary. However, with respect to the electrophile, most of these reactions are nucleophilic substitutions, and what was said in Chapter 10 is pertinent to them.

1-12 Friedel–Crafts Alkylation
Alkylation or Alkyl-de-hydrogenation

$$ArH + RCl \xrightarrow{AlCl_3} ArR$$

[214]Groves tein; Aprahamian; Bryan; Gnanapragasam; Kilby; McKelvey; Sullivan *J. Am. Chem. Soc.* **1973,** *95,* 4261.

[215]Ogata; Urasaki *J. Chem. Soc. C* **1970,** 1689.

[216]Arotsky; Butler; Darby *J. Chem. Soc. C* **1970,** 1480.

[216a]Galli *J. Org. Chem.* **1991,** *56,* 3238.

[217]For a monograph on fluorinating agents, see German; Zemskov *New Fluorinating Agents in Organic Synthesis*; Springer: New York, 1989. For reviews of F_2 in organic synthesis, see Purrington; Kagen; Patrick *Chem. Rev.* **1986,** *86,* 997-1018; Grakauskas, *Intra-Sci. Chem. Rep.* **1971,** *5,* 85-104. For a review of fluoroaromatic compounds, see Hewitt; Silvester *Aldrichimica Acta* **1988,** *21,* 3-10.

[218]Grakauskas *J. Org. Chem.* **1970,** *35,* 723; Cacace; Giacomello; Wolf *J. Am. Chem. Soc.* **1980,** *102,* 3511; Stavber; Zupan *J. Org. Chem.* **1983,** *48,* 2223. See also Purrington; Woodard *J. Org. Chem.* **1991,** *56,* 142.

[219]Zweig; Fischer; Lancaster *J. Org. Chem.* **1980,** *45,* 3597.

[220]Ip; Arthur; Winans; Appelman *J. Am. Chem. Soc.* **1981,** *103,* 1964; Stavber; Zupan *J. Org. Chem.* **1985,** *50,* 3609; Appelman; Basile; Hayatsu *Tetrahedron* **1984,** *40,* 189; Patrick; Darling *J. Org. Chem.* **1986,** *51,* 3242.

[221]See Hebel; Lerman; Rozen *Bull. Soc. Chim. Fr.* **1986,** 861; Visser; Bakker; van Halteren; Herscheid; Brinkman; Hockstra *J. Org. Chem.* **1986,** *51,* 1886.

[222]Shaw; Hyman; Filler *J. Am. Chem. Soc.* **1969,** *91,* 1563, **1970,** *92,* 6498, *J. Org. Chem.* **1971,** *36,* 2917; Mackenzie; Fajer *J. Am. Chem. Soc.* **1970,** *92,* 4994; Filler *Isr. J. Chem.* **1978,** *17,* 71.

[223]Singh; DesMarteau; Zuberi; Witz; Huang *J. Am. Chem. Soc.* **1987,** *109,* 7194.

[224]Barton; Ganguly; Hesse; Loo; Pechet *Chem. Commun.* **1968,** 806; Kollonitsch; Barash; Doldouras *J. Am. Chem. Soc.* **1970,** *92,* 7494; Patrick; Cantrell; Chang *J. Am. Chem. Soc.* **1979,** *101,* 7434; Fifolt; Olczak; Mundhenke; Bieron *J. Org. Chem.* **1985,** *50,* 4576. For a review of this reagent, see Barton *Pure. Appl. Chem.* **1977,** *49,* 1241-1249.

−70°C.[256] Rearrangement could also occur *after* formation of the product, since alkylation is reversible (see **1-37**).[257]

See **4-21** and **4-23** for free-radical alkylation.

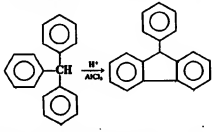
OS **I**, 95, 548; **II**, 151, 229, 232, 236, 248; **III**, 343, 347, 504, 842; **IV**, 47, 520, 620, 665, 702, 898, 960; **V**, 130, 654; **VI**, 109, 744.

1-13 Friedel–Crafts Arylation. The Scholl Reaction
De-hydrogen-coupling

$$2ArH \xrightarrow[H^+]{AlCl_3} Ar{-}Ar + H_2$$

The coupling of two aromatic molecules by treatment with a Lewis acid and a proton acid is called the *Scholl reaction*.[258] Yields are low and the synthesis is seldom useful. High temperatures and strong-acid catalysts are required, and the reaction fails for substrates that are destroyed by these conditions. Because the reaction becomes important with large fused-ring systems, ordinary Friedel–Crafts reactions (**1-12**) on these systems are rare. For example, naphthalene gives binaphthyl under Friedel–Crafts conditions. Yields can be increased by the addition of a salt such as $CuCl_2$ or $FeCl_3$, which acts as an oxidant.[259]

Intramolecular Scholl reactions, e.g.,



are much more successful than the intermolecular kind. The mechanism is not clear, but it may involve attack by a proton to give an arenium ion of the type **9** (p. 504), which would be the electrophile that attacks the other ring.[260] Sometimes arylations have been accomplished by treating aromatic substrates with particularly active aryl halides, especially fluorides. For free-radical arylations, see reactions **4-18** to **4-22**.

OS **IV**, 482. Also see OS **V**, 102, 952.

1-14 Friedel–Crafts Acylation
Acylation or Acyl-de-hydrogenation

$$ArH + RCOCl \xrightarrow{AlCl_3} ArCOR$$

The most important method for the preparation of aryl ketones is known as *Friedel–Crafts acylation*.[261] The reaction is of wide scope. Reagents used[262] are not only acyl halides but

[256]For a review of the use of isotopic labeling to study Friedel–Crafts reactions, see Roberts; Gilson *Isot. Org. Chem.* **1980**, *5*, 103-145.

[257]For an example, see Lee; Hamblin; Uthe *Can. J. Chem.* **1964**, *42*, 1771.

[258]For reviews, see Kovacic; Jones *Chem. Rev.* **1987**, *87*, 357-79; Balaban; Nenitzescu, in Olah, Ref. 225, vol. 2, pp. 979-1047.

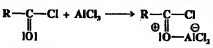
[259]Kovacic; Koch *J. Org. Chem.* **1963**, *28*, 1864, **1965**, *30*, 3176; Kovacic; Wu *J. Org. Chem.* **1961**, *26*, 759, 762. For examples, with references, see Larock, Ref. 171, pp. 45-46.

[260]For a discussion, see Clowes *J. Chem. Soc. C* **1968**, 2519.

[261]For reviews of Friedel–Crafts acylation, see Olah *Friedel–Crafts and Related Reactions*; Wiley: New York, 1963-1964, as follows: vol. 1, Olah, pp. 91-115; vol. 3, Gore, pp. 1-381; Peto, pp. 535-910; Sethna, pp. 911-1002; Jensen; Goldman, pp. 1003-1032. For another review, see Gore *Chem. Ind. (London)* **1974**, 727-731.

[262]For a list of reagents, with references, see Larock, Ref. 171, pp. 703-704.

also carboxylic acids, anhydrides, and ketenes. Carboxylic esters usually give predominant alkylation (see 1-12). R may be aryl as well as alkyl. The major disadvantages of Friedel–Crafts alkylation are not present here. Rearrangement of R is never found, and, because the RCO group is deactivating, the reaction stops cleanly after one group is introduced. All four acyl halides can be used, though chlorides are most commonly employed. The order of activity is usually, but not always, I > Br > Cl > F.[263] Catalysts are Lewis acids, similar to those in reaction 1-12, but in acylation a little more than 1 mole of catalyst is required per mole of reagent, because the first mole coordinates with the oxygen of the reagent.[264]

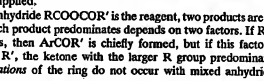


Proton acids can be used as catalysts when the reagent is a carboxylic acid. The mixed carboxylic sulfonic anhydrides $RCOOSO_2CF_3$ are extremely reactive acylating agents and can smoothly acylate benzene without a catalyst.[265] With active substrates (e.g., aryl ethers, fused-ring systems, thiophenes), Friedel–Crafts acylation can be carried out with very small amounts of catalyst, often just a trace, or even sometimes with no catalyst at all. Ferric chloride, iodine, zinc chloride, and iron are the most common catalysts when the reactions is carried out in this manner.[266]

The reaction is quite successful for many types of substrate, including fused ring systems, which give poor results in 1-12. Compounds containing ortho-para-directing groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated and give mainly or exclusively the para products, because of the relatively large size of the acyl group. However, aromatic amines give poor results. With amines and phenols there may be competition from N- or O-acylation; however, O-acylated phenols can be converted to C-acylated phenols by the Fries rearrangement (1-30). Friedel–Crafts acylation is usually prevented by meta-directing groups. Indeed, nitrobenzene is often used as a solvent for the reaction. Many heterocyclic systems, including furans, thiophenes, pyrans, and pyrroles but not pyridines or quinolines, can be acylated in good yield (however, pyridines and quinolines can be acylated by a free-radical mechanism, reaction 4-23). Gore, in Ref. 261 (pp. 36–100; with tables, pp. 105–321), presents an exhaustive summary of the substrates to which this reaction has been applied.

When a mixed anhydride RCOOCOR′ is the reagent, two products are possible—ArCOR and ArCOR′. Which product predominates depends on two factors. If R contains electron-withdrawing groups, then ArCOR′ is chiefly formed, but if this factor is approximately constant in R and R′, the ketone with the larger R group predominantly forms.[267] This means that *formylations* of the ring do not occur with mixed anhydrides of formic acid HCOOCOR.

An important use of the Friedel–Crafts acylation is to effect ring closure.[268] This can be done if an acyl halide, anhydride, or acid group is in the proper position. An example is



[263]Yamase *Bull. Chem. Soc. Jpn.* **1961**, *34*, 480; Corriu *Bull. Soc. Chim. Fr.* **1965**, 821.

[264]The crystal structures of several of these complexes have been reported: Rasmussen; Broch *Acta Chem. Scand.* **1966**, *20*, 1351; Chevrier; Le Carpentier; Weiss *J. Am. Chem. Soc.* **1972**, *94*, 5718. For a review of these complexes, see Chevrier; Weiss *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 1-10 [*Angew. Chem.* 88, 12-21].

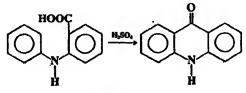
[265]Effenberger; Sohn; Epple *Chem. Ber.* **1983**, *116*, 1195. See also Keumi; Yoshimura; Shimada; Kitajima *Bull. Chem. Soc. Jpn.* **1988**, *44*, 455.

[266]For a review, see Pearson; Buehler *Synthesis* **1972**, 533-542.

[267]Edwards; Sibelle *J. Org. Chem.* **1963**, *28*, 674.

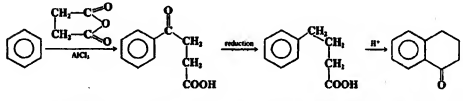
[268]For a review, see Sethna, Ref. 261. For examples, with references, see Larock, Ref. 171, pp. 704-708.

The reaction is used mostly to close 6-membered rings, but has also been done for 5- and 7-membered rings, which close less readily. Even larger rings can be closed by high-dilution techniques.[269] Tricyclic and larger systems are often made by using substrates containing one of the acyl groups on a ring. An example is the formation of acridone:



Many fused ring systems are made in this manner. If the bridging group is CO, the product is a quinone.[270] One of the most common catalysts for intramolecular Friedel–Crafts acylation is polyphosphoric acid[271] (because of its high potency), but $AlCl_3$, H_2SO_4, and other Lewis and proton acids are also used, though acylations with acyl halides are not generally catalyzed by proton acids.

Friedel–Crafts acylation can be carried out with cyclic anhydrides,[272] in which case the product contains a carboxyl group in the side chain. When succinic anhydride is used, the product is $ArCOCH_2CH_2COOH$. This can be reduced (9-37) to $ArCH_2CH_2CH_2COOH$, which can then be cyclized by an internal Friedel–Crafts acylation. The total process is called the *Haworth reaction*:[273]



The mechanism of Friedel–Crafts acylation is not completely understood, but at least two mechanisms probably operate, depending on conditions.[274] In most cases the attacking species is the acyl cation, either free or as an ion pair, formed by[275]

$$RCOCl + AlCl_3 \longrightarrow RCO^+ + AlCl_4^-$$

If R is tertiary, RCO^+ may lose CO to give R^+, so that the alkylarene ArR is often a side product or even the main product. This kind of cleavage is much more likely with relatively unreactive substrates, where the acylium ion has time to break down. For example, pivaloyl chloride Me_3CCOCl gives the normal acyl product with anisole, but the alkyl product Me_3CPh with benzene. In the other mechanism an acyl cation is not involved, but the 1:1 complex attacks directly.[276]

[269]For example, see Schubert; Sweeney; Latourette *J. Am. Chem. Soc.* **1954**, *76*, 5462.

[270]For discussions, see Nanuts; Maruyama. In Patai; Rappoport *The Chemistry of the Quinonoid Compounds*, vol. 2, pt. 1; Wiley: New York, 1988, pp. 325-332; Thomson. in Patai *The Chemistry of the Quinonoid Compounds*, vol. 1, pt. 1; Wiley: New York, 1974; pp. 136-139.

[271]For a review of polyphosphoric acid, see Rowlands, in Pizey, Ref. 199, vol. 6, 1985, pp. 156-414.

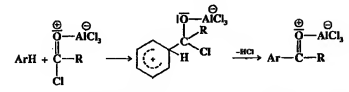
[272]For a review see Peto, Ref. 261.

[273]See Agranat; Shih *J. Chem. Educ.* **1976**, *53*, 488.

[274]For a review of the mechanism see Taylor *Electrophilic Aromatic Substitution*, Ref. 1, pp. 222-237.

[275]After 2 min, exchange between PhCOCl and $Al(^{36}Cl)_3$ is complete: Oulevey; Susz *Helv. Chim. Acta* **1964**, *47*, 1828.

[276]For example, see Corriu; Coste *Bull. Soc. Chim. Fr.* **1967**, 2562, 2568, 2574; **1969**, 3272; Corriu; Dore; Thomassin *Tetrahedron* **1971**, *27*, 5601, 5819; Tan; Brownstein *J. Org. Chem.* **1983**, *48*, 302.

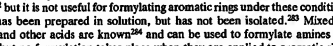


Free-ion attack is more likely for sterically hindered R.[277] The ion CH_3CO^+ has been detected (by ir spectroscopy) in the liquid complex between acetyl chloride and aluminum chloride, and in polar solvents such as nitrobenzene; but in nonpolar solvents such as chloroform, only the complex and not the free ion is present.[278] In any event, 1 mole of catalyst certainly remains complexed to the product at the end of the reaction. When the reaction is performed with $RCO^+ SbF_6^-$, no catalyst is required and the free ion[279] (or ion pair) is undoubtedly the attacking entity.[280]

OS I, 109, 353, 476, 517; II, 3, 8, 15, 81, 156, 169, 304, 520, 569; III, 6, 14, 23, 53, 109, 183, 248, 272, 593, 637, 761, 798; IV, 8, 34, 88, 898, 900; V, 111; VI, 34, 618, 625.

Reactions 1-15 through 1-18 are direct formylations of the ring.[281] Reaction 1-14 has not been used for formylation, since neither formic anhydride nor formyl chloride is stable at ordinary temperatures. Formyl chloride has been shown to be stable in chloroform solution for 1 hr at $-60°C$,[282] but it is not useful for formylating aromatic rings under these conditions. Formic anhydride has been prepared in solution, but has not been isolated.[283] Mixed anhydrides of formic and other acids are known[284] and can be used to formylate amines (see 0-53) and alcohols, but no formylation takes place when they are applied to aromatic rings. See 3-17 for a nucleophilic method for the formylation of aromatic rings.

1-15 Formylation with Disubstituted Formamides
Formylation or Formyl-de-hydrogenation



The reaction with disubstituted formamides and phosphorus oxychloride, called the *Vilsmeier* or the *Vilsmeier–Haack reaction*, is the most common method for the formylation of aromatic rings.[285] However, it is applicable only to active substrates, such as amines and phenols. Aromatic hydrocarbons and heterocycles can also be formylated, but only if they are much more active than benzene (e.g., azulenes, ferrocenes). Though N-phenyl-N-methylform-

[277]Yamase *Bull. Chem. Soc. Jpn.* **1961**, *34*, 484; Gore *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1627; Satchell *J. Chem. Soc.* **1961**, 5404.

[278]Cook *Can. J. Chem.* **1959**, *37*, 48; Cassimatis; Bonnin; Theophanides *Can. J. Chem.* **1970**, *48*, 3860.

[279]Crystal structures of solid $RCO^+ SbF_6^-$ salts have been reported: Boer *J. Am. Chem. Soc.* **1968**, *90*, 6706; Chevrier; Le Carpentier; Weiss *Acta Crystallogr., Sect. B* **1972**, *28*, 2673, *J. Am. Chem. Soc.* **1972**, *94*, 5718.

[280]Olah; Kuhn; Flood; Hardie *J. Am. Chem. Soc.* **1964**, *86*, 2203; Olah; Liu; Germain *Synthesis* **1974**, 895. For a review of acylium salts in organic synthesis, see Al-Talib; Tashtoush *Org. Prep. Proced. Int.* **1990**, *22*, 1-36.

[281]For a review, see Olah; Kuhn, in Olah, Ref. 261, vol. 3, 1964, pp. 1153-1256. For a review of formylating agents, see Olah; Ohannesian; Arvanaghi *Chem. Rev.* **1987**, *87*, 671-686. For a list of reagents, with references, see Larock, Ref. 171, pp. 702-703.

[282]Staab; Datta *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 132 [*Angew. Chem.* **1963**, *75*, 1203].

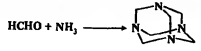
[283]Olah; Vankar; Arvanaghi; Sommer *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 614 [*Angew. Chem. 91*, 649]; Schijf; Scheeren; van Es; Stevens *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 594.

[284]Stevens; van Es *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 863.

[285]For a review, see Jutz *Adv. Org. Chem.* **1976**, *9*, pt. 1, 225-342.

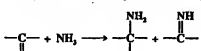
D. Attack by NH_2, NHR, or NR_2 (Addition of NH_3, RNH_2, R_2NH)

6-13 The Addition of Ammonia to Aldehydes and Ketones
Formaldehyde–hexamethylenetetramine transformation



11

The addition of ammonia[141] to aldehydes or ketones does not generally give useful products. According to the pattern followed by analogous nucleophiles, the initial products would be expected to be *hemiaminals*[142] (also called "aldehyde ammonias") (**12**) and/or imines (**13**):

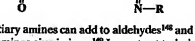


12 **13**

However, these compounds are generally unstable. Most imines with a hydrogen on the nitrogen spontaneously polymerize.[143] Stable hemiaminals can be prepared from polychlorinated and polyfluorinated aldehydes and ketones, and diaryl ketones do give stable imines $Ar_2C{=}NH$.[144] Aside from these, when stable compounds *are* prepared in this reaction, they are the result of combinations and condensations of one or more molecules of **12** and/or **13** with each other or with additional molecules of ammonia or carbonyl compound. The most important example of such a product is hexamethylenetetramine[145] (**11**), prepared from ammonia and formaldehyde.[146] Aromatic aldehydes give hydrobenzamides $ArCH(N{=}CHAr)_2$ derived from three molecules of aldehyde and two of ammonia.[147]

OS II, 214, 219; IV, 451; VI, 664, 976. Also see OS III, 471; V, 897.

6-14 The Addition of Amines to Aldehydes and Ketones
Alkylimino-de-oxo-bisubstitution



Primary, secondary, and tertiary amines can add to aldehydes[148] and ketones to give different kinds of products. Primary amines give imines.[149] In contrast to imines in which the nitrogen

[141]For a review of this reagent in organic synthesis, see Jeyaraman, in Pizey *Synthetic Reagents*, vol. 5; Wiley: New York, 1983, pp. 9-83.

[142]These compounds have been detected by ^{13}C nmr: Chudek; Foster; Young *J. Chem. Soc., Perkin Trans. 2* **1985**, 1285.

[143]Methanimine $CH_2{=}NH$ is stable in solution for several hours at −95°C, but rapidly decomposes at −80°C: Braillon; Lasne; Ripoll; Denis *Nouv. J. Chim.* **1982**, *6*, 121. See also Bock; Dammel *Chem. Ber.* **1987**, *120*, 1961.

[144]Verardo; Ghiamanini; Strazzolini; Poiana *Synth. Commun.* **1988**, *18*, 1501.

[145]For a review of this compound, see Blažević; Kolbah; Belin; Šunjić; Kajfež *Synthesis* **1979**, 161-176.

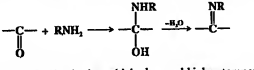
[146]For a discussion of the mechanism, see Nielsea; Moore; Ogan; Atkins *J. Org. Chem.* **1979**, *44*, 1678.

[147]Ogata; Kawasaki; Okumura *J. Org. Chem.* **1964**, *29*, 1985; Crowell; McLeod *J. Org. Chem.* **1967**, *32*, 4030.

[148]For a review of the reactions between amines and formaldehyde, see Farrar *Rec. Chem. Prog.* **1968**, *29*, 85-101.

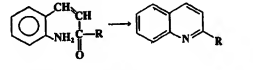
[149]For reviews of reactions of carbonyl compounds leading to the formation of C=N bonds, see Dayagi; Degani, in Patai *The Chemistry of the Carbon–Nitrogen Double Bond*; Ref. 40, pp. 64-83; Reeves, in Patai, Ref. 2, pp. 600-614.

is attached to a hydrogen (6-13), these imines are stable enough for isolation. However, in some cases, especially with simple R groups, they rapidly decompose or polymerize unless there is at least one aryl group on the nitrogen or the carbon. When there is an aryl group, the compounds are quite stable. They are usually called *Schiff bases*, and this reaction is the best way to prepare them. The reaction is straightforward and proceeds in high yields. The initial N-substituted hemiaminals[150] lose water to give the stable Schiff bases:



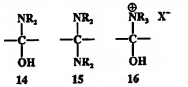
In general, ketones react more slowly than aldehydes, and higher temperatures and longer reaction times are often required.[151] In addition, the equilibrium must often be shifted, usually by removal of the water, either azeotropically by distillation, or with a drying agent such as $TiCl_4$,[152] or with a molecular sieve.[153]

The reaction is often used to effect ring closure.[154] The *Friedländer quinoline synthesis*[155] is an example:



Pyrylium ions react with ammonia or primary amines to give pyridinium ions[156] (see p. 354).

When secondary amines are added to aldehydes or ketones, the initially formed N,N-disubstituted hemiaminals (14) cannot lose water in the same way, and it is possible to isolate them.[157] However, they are generally unstable, and under the reaction conditions



14 15 16

aminal

usually react further. If no α hydrogen is present, 14 is converted to the more stable *aminal* (15).[158] However, if an α hydrogen is present, water (from 14) or RNH_2 (from 15) can be lost in that direction to give an enamine:[159]

[150]Some of these have been observed spectrally; see Forlani; Marianucci; Todesco *J. Chem. Res.* (*S*) 1984, 126.

[151]For improved methods, see Morimoto; Sekiya *Chem. Lett.* 1985, 1371; Eisch; Sanchez *J. Org. Chem.* 1986, *51*, 1848.

[152]Weingarten; Chupp; White *J. Org. Chem.* 1967, *32*, 3246.

[153]Bonnett; Emerson *J. Chem. Soc.* 1965, 4508; Roelofsen; van Bekkum *Recl. Trav. Chim. Pays-Bays* 1972, *91*, 605.

[154]For a review of such ring closures, see Katritzky; Ostercamp; Yousaf *Tetrahedron* 1987, *43*, 5171-5186.

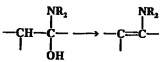
[155]For a review, see Cheng; Yan *Org. React.* 1982, *28*, 37-201.

[156]For a review, see Zvezdina; Zhadonva; Dorofeenko *Russ. Chem. Rev.* 1982, *51*, 469-484.

[157]For example, see Duhamel; Cantacuzène *Bull. Soc. Chim. Fr.* 1962, 1843.

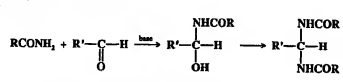
[158]For a review of aminals, see Duhamel, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 2; Wiley: New York, 1982, pp. 849-907.

[159]For reviews of the preparation of enamines, see Haynes; Cook, in Cook, Ref. 45, pp. 103-163; Pitacco; Valentin, in Patai, Ref. 158, pt. 1, pp. 623-714.



This is the most common method[160] for the preparation of enamines and usually takes place when an aldehyde or ketone containing an α hydrogen is treated with a secondary amine. The water is usually removed azeotropically or with a drying agent,[161] but molecular sieves can also be used.[162] Secondary amine perchlorates react with aldehydes and ketones to give iminium salts (**2**, p. 885).[163] Tertiary amines can only give salts (**16**).

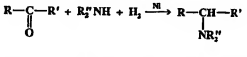
Amides can add to aldehydes in the presence of bases (so the nucleophile is actually $RCONH^-$) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides:[164]



If the R′ group contains an α hydrogen, water may split out.

OS I, 80, 355, 381; II, 31, 49, 65, 202, 231, 422; III, 95, 328, 329, 332, 358, 374, 513, 753, 827; IV, 210, 605, 638, 824; V, 191, 277, 533, 567, 627, 703, 716, 736, 758, 808, 941, 1070; VI, 5, 448, 474, 496, 520, 526, 592, 601, 818, 901, 1014; VII, 8, 135, 144, 473; **65**, 108, 119, 146, 183; **66**, 133, 142, 203; **68**, 206. Also see OS IV, 283, 464; VII, 197; **66**, 52; **69**, 55, 158.

6-15 Reductive Alkylation of Ammonia or Amines
Hydro,dialkylamino-de-oxo-bisubstitution



When an aldehyde or a ketone is treated with ammonia or a primary or secondary amine in the presence of hydrogen and a hydrogenation catalyst (heterogeneous or homogeneous), *reductive alkylation* of ammonia or the amine (or *reductive amination* of the carbonyl compound) takes place.[165] The reaction can formally be regarded as occurring in the following manner (shown for a primary amine), which probably does correspond to the actual sequence of steps:[166]

[160]For another method, see Katritzky; Long; Luo; Jozwiak *Tetrahedron* **1996**, *46*, 8153.
[161]For example, $TiCl_4$: White; Weingarten *J. Org. Chem.* **1967**, *32*, 213; Kuo; Daly *J. Org. Chem.* **1970**, *35*, 1861; Nilsson; Carlson *Acta Chem. Scand. Sect. B* **1964**, *38*, 523.
[162]Brannock; Bell; Burpitt; Kelly *J. Org. Chem.* **1964**, *29*, 801; Taguchi; Westheimer *J. Org. Chem.* **1971**, *36*, 1570; Roelofsen; van Bekkum, Ref. 153; Carlson; Nilsson; Strömqvist *Acta Chem. Scand., Ser. B* **1983**, *37*, 7.
[163]Leonard; Paukstelis *J. Org. Chem.* **1964**, *29*, 3021.
[164]For reviews, see Challis; Challis, in Zabicky, Ref. 65, pp. 754-759; Zaugg; Martin *Org. React.* **1965**, *14*, 52-269, pp. 91-95, 104-112. For a discussion, see Gilbert *Synthesis* **1972**, 30.
[165]For reviews, see Rylander *Hydrogenation Methods*; Academic Press: New York, 1985, pp. 82-93; Klyuev; Khidekel *Russ. Chem. Rev.* **1980**, *49*, 14-27; Rylander, *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967, pp. 291-303.
[166]See, for example, Le Bris; Lefebvre; Coussemant *Bull. Soc. Chim. Fr.* **1964**, 1366, 1374, 1584, 1594.